application is also a continuation of 09/780,650, filed February 12, 2001, which is a continuation of 09/436,610, filed November 9, 1999, abandoned, which is also a continuation of 09/243,158, filed February 2, 1999. Each of the above-referenced applications is incorporated herein in its entirety.

Please rewrite Page 1, paragraph 2 as follows:

Cell mitosis is a multi-step process that includes cell division and replication (Alberts, B. et al. In *The Cell*, pp. 652-661 (1989); Stryer, E. *Biochemistry* (1988)). Mitosis is characterized by the intracellular movement and segregation of organelles, including mitotic spindles and chromosomes. Organelle movement and segregation are facilitated by the polymerization of the cell protein tubulin. Microtubules are formed from α and β tubulin polymerization and the hydrolysis of guanosine triphosphate (GTP). Microtubule formation is important for cell mitosis, cell locomotion, and the movement of highly specialized cell structures such as cilia and flagella.

Please rewrite Page 2, last paragraph, as follows:

I have discovered that certain compounds within the scope of the general formulae set forth below in the claims are useful for treating mammalian diseases characterized by undesired cell mitosis. Without wishing to bind myself to any particular theory, such compounds generally inhibit microtubule formation and tubulin polymerization and/or depolymerization. Compounds within the general formulae having said inhibiting activity are preferred. Preferred compositions may also exhibit a change (increase or decrease) in estrogen receptor binding, improved absorbtion, transport (e.g. through blood-brain barrier and cellular membranes),

biological stability, or decreased toxicity. I have also discovered certain compounds useful in the method, as described by the general formulae of the claims.

Q3

On page 3, please delete the second full paragraph.

Please rewrite page 3, line 29, as follows:

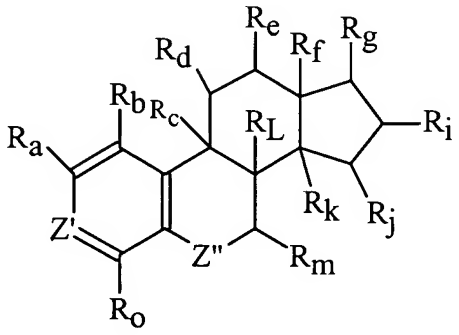
BRIEF DESCRIPTION OF THE DRAWING

Q4

On page 3, please delete the fourth paragraph.

Please rewrite page 4, third paragraph, as follows:

As described below, compounds that are useful in accordance with the invention include novel estradiol derivatives that bind tubulin, inhibit microtubule formation or exhibit anti-mitotic properties. Specific compounds according to the invention are described below.



wherein:

I. R_a-R_o are defined as follows:

A) each R_a, R_b, R_c, R_d, R_e, R_f, R_i, R_j, R_k, R_L, R_m, R_o, independently is $-R_1$, $-OR_1$, $-OCOR_1$, $-SR_1$, -F, $-NHR_2$, -Br, or -I; and R_g is $-R_1$,

Q5

-OR_1, -$OCOR_1$, -SR_1, -F, -NHR_2, -Br, -I, or -C≡CH;

or

B) each R_a, R_b, R_c, R_f, R_k, R_L, R_o, independently is -R_1, -OR_1, -$OCOR_1$, -SR_1, -F, -NHR_2, -Br, or -I; and each R_d, R_e, R_i, R_j, R_m, independently is =O, -R_1, -OR_1, -$OCOR_1$, -SR_1, -F, NHR_2, -Br or -I; and R_g is =O, -R_1, -OR_1, -$OCOR_1$, -SR_1, -F, -NHR_2, -Br, -I, or -C≡CH;

and

II. Z' is defined as follows:

A) Z' is X, where X is >COR_1, >C(=O)-R_1 [printed as >CC-R_1 with O double-bonded above the second C], >C(=O)-OR_1 [printed as >CC-OR_1 with O double-bonded above the second C],

>C(OH)H-R_1 [printed as >CCH-R_1 with OH above the second C], or >C(OH)H-OR_1 [printed as >CCH-OR_1 with OH above the second C];

or

B) Z' is =C(R_n)-X'- or -X'-C(R_n)= [printed with R_n below the C],
where R_n is -R_1, -OR_1, -SR_1, -F, -NHR_2, -Br or -I;

and X' is X, as defined above; or X' is >C=O;

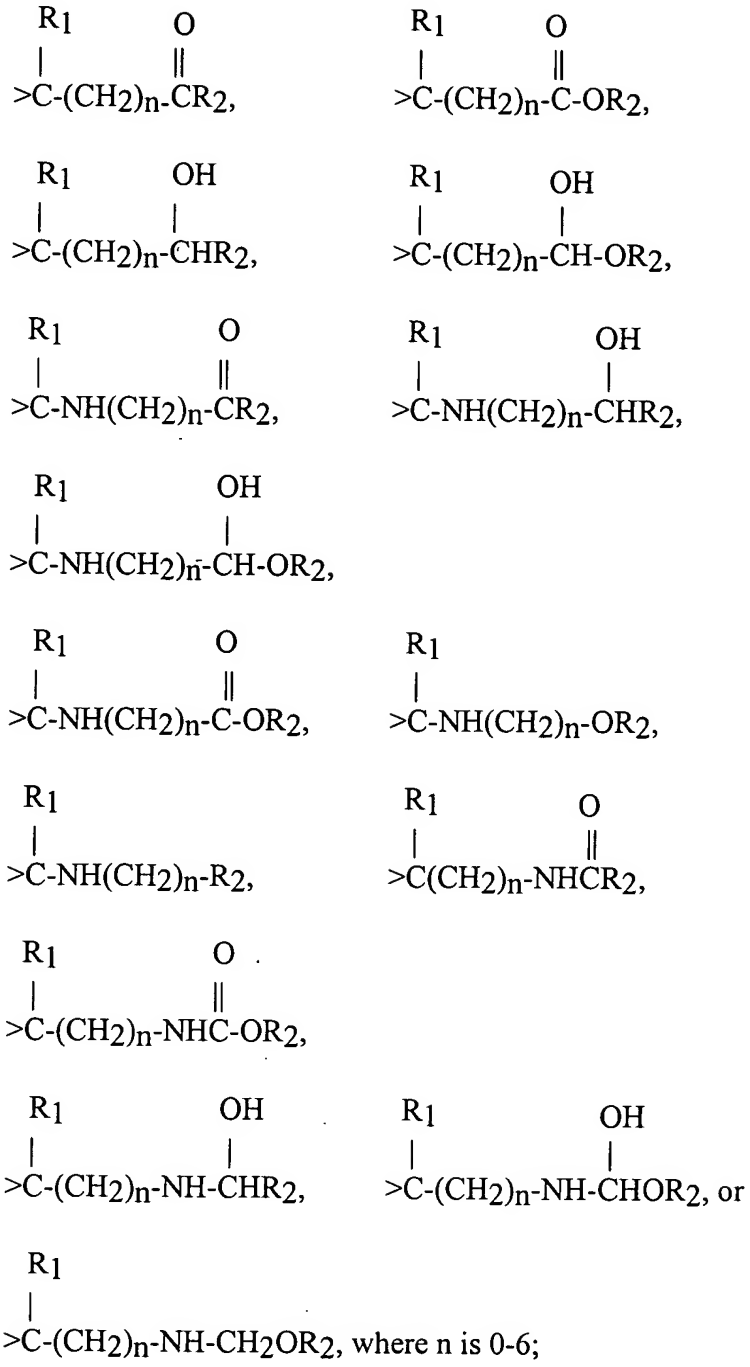
and

III. Z" is defined as follows:

A) Z" is Y, where Y is -O-, -N(R_1)- [printed as -N- with R_1 above], >CHR_1, >C=O,

>C(R_1)-$(CH_2)_nOR_2$, [printed with R_1 above the C]

a5



or

B) Z" is -Y-CH- or -CH-Y- where Rp
| |
Rp Rp

is -R_1, OR_1, -SR_1, -F, -NHR_2, -Br or -I and Y is defined as in III(A);

and

IV. provided that when each R_b, R_c, R_d, R_e, R_i, R_j, R_k, R_L, R_m and R_o is H;

R_f is $-CH_3$;

Rg is -OH;

Z' is $>COH$; and

Z" is $>CH_2$;

then R_a is not -H;

where, in each formula set forth above, each R_1 and R_2 independently is -H; or a substituted or unsubstituted alkyl, alkenyl or alkynyl group of up to 6 carbons. Those skilled in the art will appreciate that the invention extends to other compounds within the formulae given in the claims below, having the described characteristics. These characteristics can be determined for each test compound using the assays detailed below and elsewhere in the literature.

Please rewrite page 4, paragraph 4, as follows:

Without wishing to bind myself to specific mechanisms or theory, it appears that certain compounds that are known to inhibit microtubule formation, bind tubulin and exhibit anti-mitotic properties such as colchicines and combretastatin A-4 share certain structural similarities with estradiol. Fig. 3 illustrates the molecular formulae of estradiol, colchicines, combretastatin A-4, and improved estradiol derivatives that bind tubulin, inhibit microtubule assembly and exhibit anti-mitotic properties. Molecular formulae are drawn and oriented to emphasize structural similarities between the ring structures of colchicines, combretastatin A-4, estradiol, and certain estradiol derivatives. Estradiol derivatives are made by incorporating colchicines or combretastatin A-4 structural motifs into the steroidal backbone of estradiol.